PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Roberts et al.

Serial No.: 10/655,547

Filed: September 4, 2003

For: COMPOSITIONS AND METHODS FOR EARLY PREGNANCY DIAGNOSIS

Group Art Unit: 1641

Examiner: Cheu, Changhwa Jacob

Atty. Dkt. No.: UVMO:003USC1

CERTIFICATE OF ELECTRONIC SUBMISSION

Date of Submission: June 12, 2006

BRIEF ON APPEAL

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Mail Stop Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Appellants hereby submit this Appeal Brief. The date for filing this Brief is June 12, 2006. The fees for filing this Appeal Brief are attached. However, should any additional fees become due under 37 C.F.R. §§ 1.16 to 1.21 for any reason relating to the enclosed materials, or should an overpayment be made, the Commissioner is authorized to deduct or credit said fees from or to Fulbright & Jaworski Deposit Account No. 50-1212/UVMO:003USC1.

I. REAL PARTY IN INTEREST

The Real Party in Interest is the assignee, The Curators of the University of Missouri.

II. RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences for related cases.

III. STATUS OF CLAIMS

Original claims 1-181 were canceled and claims 182-196 added via a preliminary amendment during prosecution. Claims 182-196 are currently pending and have been finally rejected. A copy of the appealed claims is provided in the Claims Appendix.

IV. STATUS OF AMENDMENTS

No amendments were made subsequent to the Final Office Action.

V. SUMMARY OF CLAIMED SUBJECT MATTER

The claimed invention relates to methods for detecting pregnancy comprising detection of pregnancy associated antigens (PAGs). Specification from page 5, line 1 to page 7, line 3. The PAGs are present early in pregnancy and undetectable at about two months post-partum. Specification at page 4, line 20, to page 5, line 6.

VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

(A) Were claims 182-196 properly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement?

(B) Were claims 182-196 properly rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement?

VII. ARGUMENT

A. The Claims Satisfy the Written Description Requirement of 35 U.S.C. §112, First Paragraph

Claims 182-196 stand rejected for an asserted lack of adequate written description in the specification under 35 U.S.C. §112, first paragraph. In particular, the Examiner asserts that the specification does not describe all PAGs required to practice the method of claim 182 in a manner that satisfies either the *Lilly* or *Enzo* standards. *University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 43 U.S.P.Q.2d 1398 (Fed. Cir. 1997); *Enzo Biochem. Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 63 U.S.P.Q.2d 1609 (Fed. Cir. 2002). For example, the Examiner states that the specification does not provide the complete structure of any PAG, does not disclose a "representative number" of species of PAGs, does not provide any physical or chemical characteristics of the PAGs, and does not provide any physical or chemical characteristics coupled with a known or disclosed correlation between structure and function. Appellants traverse this rejection as the claims are fully supported as described below.

1. The Specification Describes PAGs Supporting the Full Claim Scope

Contrary to the Examiner's assertion that the present specification does not provide the complete structure of ***any*** PAG (Final Action, page 4), Appellants note that the specification discloses both cDNA and amino acid sequences of numerous bovine PAGs that are present early in pregnancy and are undetectable at about two months post-partum. For example, the specification provides sequence listings for the amino acid and nucleic acid sequences for BoPAGs 4, 6, 7, 16, 17, 20 and 21, each of which the Examiner acknowledges is a PAG that is

present early in pregnancy and is undetectable at about two months post-partum. *See e.g.,* Specification, page 10, line 10, to page 13, line 2; Final Action, page 10.

Thus, the specification provides the complete structure of at least seven PAGs that the Examiner has acknowledged fall within the scope of the claims. Final Action, page 4. Accordingly, the Examiner's assertion that the present specification does not provide the complete structure of any PAG is without merit and cannot form the basis of the present rejection.

2. The PAGs Disclosed are Representative of the Claim Scope

The Examiner has also alleged that the Specification does not disclose a "representative number" of species of PAGs. Appellants respectfully note that in *Lilly*, the court stated that "[a] description of a genus of cDNAs may be achieved by means of a recitation of ***a representative number*** of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." 119 F.3d at 1569 (emphasis added). Appellants are ***not*** required to disclose ***every species*** encompassed by their claims even in an unpredictable art. *Id.* In contrast to this legal precedent, the Examiner appears to be applying a standard that requires recitation of the structural features of every species within the genus.

As discussed above, the specification provides the structure of ***seven*** PAGs that the Examiner acknowledges are present early in pregnancy and are undetectable at about two months post-partum. If the Examiner has a basis for asserting that this is not a representative number of species within the genus of bovine PAGs that are present early in pregnancy and are undetectable at about two months post-partum, then the Examiner should be able to explain what number would be representative. No such basis or number has been provided. The Examiner's vague reference to "structural diversities" among different PAGs fails to substantiate a rejection on the

grounds that the present specification does not disclose "a representative number" of species under the *Lilly* standard. Appellants respectfully submit that the *Lilly* standard has been satisfied in this regard at least by the ***seven*** provided PAGs.

3. The Disclosure is Commensurate with the Claims

The Examiner asserts that "…it is not mainly the number, i.e. how many PAGs, is disclosed in the specification. It rests also in the correlation of structure and functionality." Final Action, page 7. Appellants respectfully assert that the working examples and figures describe just such a correlation of structure (disclosed sequences and sequence comparisons) and functionality (appropriately temporally defined expression in appropriate tissues) that allow one of skill in the art to identify PAGs. It also appears that the Examiner has misunderstood the "functionality" of PAGs for the purpose of the present claims and as known in the art. Specifically, PAGs are not defined, for instance, by a shared enzymatic activity that might be studied *e.g.* via site-directed mutagenesis. Final Action, page 7. Indeed, the art clearly indicates that many PAGs would not be expected to display aspartic proteinase activity, such as of pepsin, to which they share some degree of sequence similarity (*e.g.* Xie *et al.*, "The diversity and evolutionary relationships of the pregnancy-associated glycoproteins, an aspartic proteinase subfamily consisting of many trophoblast-expressed genes." *Proc Natl Acad Sci USA*, 94:12809–12816, 1997; cited as reference C41 in the IDS form 1449 filed October 22, 2003). In short, the described conserved regions of PAGs allow identification of members of this claimed genus to function as early markers for detection of pregnancy in bovine animals. Since these PAGs are naturally occurring proteins in the bovine placenta, their "function" for the purpose of the claimed invention would not be studied by one of skill in the art via site directed mutation or other not further-defined "correlation" studies as suggested by the Examiner in the Final Action,

at pages 8-9. Rather, their function was studied, as disclosed in the Specification, by assessing the temporal pattern of their expression and their subsequent presence in appropriate tissues.

The Examiner has further alleged that a "…conservation comparison and/or analysis **alone** is not sufficient to establish the full scope of the genus" (emphasis added; Final Action, page 9). Appellants respectfully submit that the disclosure clearly includes not only a "conservation analysis" (*e.g.* Example 2), but also includes, as noted above, a functional analysis (*e.g.* Examples 3-4 at pages 62-67) including data on the timing of PAG expression and presence in placental tissue. Further, the Examiner's comments here regarding BoPAG1 are inapposite, in that, as acknowledged by the Examiner, use of BoPAG1 is not within the scope of the claimed methods for detecting early pregnancy in bovine animals.

The Examiner has alleged that the Specification does not provide any physical or chemical characteristics of the PAGs, and does not provide any physical or chemical characteristics coupled with a known or disclosed correlation between structure and function. Appellants note in response that the Specification describes a number of physical or chemical characteristics of PAGs (See, *e.g.* Abstract; Specification, pages 19-26; and Examples 1-3 at pages 59-65. Thus, for instance, based on the known characteristics of several PAGs, several novel BoPAGs were cloned from bovine placental tissues (*e.g.* Examples 1-3) that share identity at the amino acid level, and, importantly, are expressed in appropriate tissues and in an appropriate temporal manner, present early in pregnancy and undetectable at about two months post-partum, such that they may be identified as BoPAGs that could be useful in the claimed methods for early detection of pregnancy in bovine animals.

Per *Enzo*, the specification can show that the claimed invention is complete "by disclosure of sufficiently detailed, relevant identifying characteristics… *i.e.*, complete or partial

structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." 296 F.3d at 1324. In other words, while structural formulas such as those of the PAGs provided in the specification provide a convenient method of demonstrating possession of specific molecules, ***other identifying characteristics or combinations may demonstrate the requisite possession***. *See* MPEP § 2163(II)(A)(3)(a). Here, the present specification adequately describes detecting at least one pregnancy associated antigen (PAG) in the sample that is present early in pregnancy and is undetectable at about two months post-partum such that a person of ordinary skill in the art would understand that the inventors were in possession of the claimed invention at the time of filing.

The Examiner also alleges that "…one of ordinary skill in the art would not conclude that the applicant (sic) sufficiently describe a 'representative number' of such species". Final Action, page 4. In response Appellants respectfully note that no further substantiation of this allegation is given by the Examiner. Further, the Specification (*e.g.* Example 1) describes use of several known PAGs to isolate additional novel PAGs. Sequence and expression characteristics of several of these PAGs are further described in, for instance, Examples 1-3 and associated figures, as follows:

First, and as discussed above, the specification provides the structure of seven PAGs that the Examiner acknowledges are within the scope of the claims. While there is some degree of structural diversity among PAGs, there is also a high level of conservation. As shown in FIG. 4, for example, there is ***substantial identity*** among bovine PAGs at both the nucleic acid and amino acid level. This conservation is further illustrated in the sequence alignments provided in FIG. 1 and the phylogenic tree provided in FIG. 5. The alignments show both conserved regions and

indicate a common ancestry. It must further be noted that the genus of PAGs is limited because such PAGs are ***naturally produced*** by bovine animals. Specifically, the claims are directed to a method for detecting pregnancy in a bovine animal that involves detecting at least one of the aforementioned PAGs that is present in a biological sample from the animal. This situation is vastly different from the case in which a nucleic acid or polypeptide sequence is claimed without sufficiently defining the corresponding structure. In that instance the number of sequences encompassed could be boundless. Here, the genus of sequences is limited by what PAGs are produced by a bovine animal, and these sequences have been shown to be related. The biology of the animal thus dictates a finite and limited class of PAGs.

It must also be noted that the PAGs detected in the claimed method share ***both structural and functional*** characteristics. The claims require the shared functional characteristic of presence early in pregnancy and absence by about two months post-partum, which is significant in that early detection is needed given that artificial insemination is successful less than 50% of the time (see specification page 2, line 25 to page 3, line 4). The shared structural characteristics are demonstrated for instance in the alignments given in FIGs. 1 and 4 and the tree presented in FIG. 5.

The specification also teaches that, due to the homology among bovine PAGs, one can utilize nucleic acid probes or antibodies to known PAGs to screen placental tissues at various time point during pregnancy to isolate additional, novel PAGs that are present early in pregnancy and are undetectable at about two months post-partum. *See e.g.,* page 41, line 25, to page 42, line 2; page 46, lines 2-12; and page 58, line 4 to page 59, line 7. Thus, the present specification adequately describes the full scope of a method comprising detecting at least one bovine PAG in

a sample that is present early in pregnancy and is undetectable at about two months post-partum under the relevant legal standards. Reversal of the rejection is thus respectfully requested.

4. Conclusion

As explained above, Appellants have demonstrated that the present specification provides a full written description of the claimed subject matter in terms of the structure of representative PAGs within the scope of the claims. In addition, the present specification describes a combination of relevant structural and functional identifying characteristics of PAGs that are present early in pregnancy and are undetectable at about two months post-partum. Finally, it is shown, contrary to the assertions by the Examiner, that the genus of PAGs is not limitless and is in fact limited by the biology of bovine animals to a finite number of structurally and functionally related sequences. Appellants, therefore, respectfully request the reversal of this rejection.

B. The Claims Satisfy the Enablement Requirement of 35 U.S.C. §112, First Paragraph

Claims 182-196 stand rejected for lack of enablement. The Examiner acknowledges that the specification is enabling for PAGs 4, 6, 7, 16, 17, 20, and 21, but asserts that the specification is not reasonably enabling for all PAGs encompassed by the claims. Final Action, page 5. Appellants respectfully traverse.

1. The Examiner Fails to Establish a *Prima Facie* Case of Non-Enablement

The test of enablement is whether the specification teaches a person of ordinary skill in the art how to make or use the invention without undue experimentation. MPEP § 2164.01. Whether making and using a claimed invention requires undue experimentation is not a single factual determination, but rather, it is a conclusion reached by weighing all of the *Wands* factors. MPEP §2164.01(a) (citing *In re Wands*, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988)). It is

improper to conclude that a disclosure is not enabling based on an analysis of only one of the *Wands* factors while ignoring others. *Id.* Appellants respectfully submit that the Specification contains sufficient direction as well as working examples that allow one of skill in the art to practice the invention without undue experimentation.

In support of the present rejection, the Examiner merely restates the arguments for the lack of written description rejection. Specifically, the Examiner states that the specification does not provide the complete structure of any PAG, does not disclose a "representative number" of species of PAGs, does not provide any physical or chemical characteristics of the PAGs, and does not provide any physical or chemical characteristics coupled with a known or disclosed correlation between structure and function. As noted above with respect to written description, these four allegations are mistaken in that complete structure (*i.e.* sequences) of representative PAGs is in fact provided; seven species of PAGs are disclosed; and physical and chemical characteristics coupled with correlations between structure and function (insofar as relates to their use as markers for early pregnancy) are also provided. Additionally, the working examples clearly demonstrate how one of ordinary skill in the art may routinely identify BoPAGs. Thus the Examiner's allegations are insufficient to establish a *prima facie* case for lack of enablement.

Still further, the Examiner acknowledges enablement for ***seven*** PAGs within the scope of the claims. No basis has been provided to conclude why these examples alone do not demonstrate enablement for the full scope of the claims. Enablement is satisfied as long as at least one method is provided for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claims. MPEP 2164.01(b) (citing *In re Fisher*, 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (CCPA 1970)). An assertion that the disclosure is not commensurate with the scope of the claims must be supported by evidence or reasoning

substantiating the doubts advanced. *In re Dinh-Nguyen*, 181 U.S.P.Q. 46 (CCPA 1974); *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (examiner must provide a reasonable explanation as to why the scope of protection provided by a claim is not adequately enabled by the disclosure). None of these requirements have been met and thus reversal of the rejection is respectfully requested.

2. The Specification Provides an Enabling Disclosure

The present specification teaches a person of ordinary skill in the art how to make and use the invention without undue experimentation. First, the Examiner acknowledges that the specification is enabling for PAGs 4, 6, 7, 16, 17, 20, and 21. Action, p. 5. These examples alone demonstrate enablement for the full scope of the claims. Furthermore, the present specification discloses both cDNA and amino acid sequences for these and other bovine PAGs. *See e.g.,* Specification, page 10, line 4, to page 13, line 2. While different PAGs may have different amino acid sequences, Appellants again point out that there is substantial identity among bovine PAGs at both the nucleic acid and amino acid level. *See e.g.*, FIG. 1 and FIG. 5. In fact, the inventors cloned the novel, bovine PAGs disclosed in the specification using nucleic acid probes from known bovine, ovine, and porcine PAG1 and PAG2, and equine PAG cDNAs. Specification page 59, lines 24-26.

The present specification provides a detailed description of PAGs. *See e.g.,* page 18, line 27 to page 28, line 13. As appreciated by the inventors and explained in the specification, temporal expression during pregnancy can vary among PAGs. Certain PAGs, therefore, can be used for the detection of pregnancy at an early stage. *See e.g.,* Specification, page 50, lines 11-25. In addition to the specific PAGs disclosed in the specification, the specification fully describes the assays and procedures that would be used by one of skill in the art to isolate additional PAGs within the scope of the claims. See specification, *e.g.,* page 41, line. 25 to page

42, line 2; page 46, lines 2-12; and page 58, line 4, to page 59, line 7; see also 1st Declaration of Dr. Green; and 2nd Declaration of Dr. Green.

The identification of additional PAGs within the scope of the claims would require no more than routine screening, and the present specification provides ample guidance with respect to the direction of such screening by way of the working examples. While some PAGs such as BoPAG1 are not present early in pregnancy and undetectable at about two-months post-partum, these PAGs can be readily identified using routine screening as explained above according to the techniques used in the working examples. "[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." *In re Wands*, 858 at 737. Further, the presence of inoperative embodiments does not necessarily render a claim nonenabled. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984). Enablement has therefore been fully demonstrated, and reversal of this rejection is respectfully requested.

3. Conclusion

The present specification teaches a person of ordinary skill in the art how to make or use the invention without undue experimentation. The scope of enablement must only bear ***a reasonable correlation*** to the scope of the claims. MPEP § 2164.08. The Examiner fails to establish why the PAGs acknowledged to fall within the scope of the claims do not bear a reasonable correlation to the genus of PAGs that are present early in pregnancy and undetectable two-months post-partum. Second, the present specification provides a detailed description of PAGs and fully describes the assays and procedures that would be used by one of skill in the art to isolate additional PAGs that are present early in pregnancy and undetectable two-months post-partum. Appellants therefore respectfully request the reversal of this rejection.

CONCLUSION

It is respectfully submitted, in light of the above, that none of the claims are properly rejected. Therefore, Appellants request that the Board reverse the pending grounds for rejection.

Respectfully submitted,

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Date: June 12, 2006

VIII. CLAIMS APPENDIX

182. (Previously presented) A method for detecting pregnancy in a bovine animal comprising:

(a) obtaining a sample from said animal; and

(b) detecting at least one pregnancy associated antigen (PAG) in the sample that is present early in pregnancy and is undetectable at about two months post-partum; whereby detection of the PAG indicates that the animal is pregnant.

183. (Previously presented) The method of claim 182, wherein said sample is selected from the group consisting of saliva, serum, blood, milk or urine.

184. (Previously presented) The method of claim 182, wherein said detecting comprises ELISA.

185. (Previously presented) The method of claim 182, wherein said detecting comprises RIA.

186. (Previously presented) The method of claim 182, wherein said detecting comprises Western blot.

187. (Previously presented) The method of claim 182, wherein detecting is carried out by immunologic detection.

188. (Previously presented) The method of claim 187, wherein immunologic detection comprises detection with polyclonal antisera.

189. (Previously presented) The method of claim 187, wherein immunologic detection comprises detection with a monoclonal antibody preparation.

190. (Previously presented) The method of claim 182, wherein detecting comprises RNA detection.

191. (Previously presented) The method of claim 182, further comprising detecting at least two PAGs in said sample.

192. (Previously presented) The method of claim 191, further comprising detecting at least three PAGs in said sample.

193. (Previously presented) The method of claim 184, wherein said ELISA is a sandwich ELISA comprising binding the PAG to a first antibody preparation fixed to a substrate and a second antibody preparation labeled with an enzyme.

194. (Previously presented) The method of claim 193, wherein said enzyme is alkaline phosphatase or horseradish peroxidase.

195. (Previously presented) The method of claim 193, wherein said first antibody preparation is monoclonal.

196. (Previously presented) The method of claim 193, wherein said first antibody preparation is polyclonal.

IX. EVIDENCE APPENDIX

No exhibits.

X. RELATED PROCEEDINGS APPENDIX

There are no related proceedings.